A2 cont.

patient in need thereof of an effective amount of desglymidodrine and optionally, midodrine as well.--

In the Claims

Please **cancel** claims **1-75**.

Please **add** claims **76-171**.

A3

76. (New) A solid pharmaceutical composition for oral use comprising desglymidodrine or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable excipients.

77. (New) The composition according to claim 76, wherein desglymidodrine is selected from the group consisting of (±)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (± ST 1059), (+)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (+ ST 1059), (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059), and mixtures thereof.

78. (New) The composition according to claim 77, wherein desglymidodrine is (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059).

79. (New) The composition according to claim 76, wherein at least 90% w/w of desglymidodrine is (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059).

80. (New) The composition according to claim 76, wherein desglymidodrine is present in the form of a pharmaceutically acceptable salt selected from the group consisting of a salt formed between desglymidodrine and an inorganic acid and a salt formed between desglymidodrine and an organic acid.

81. (New) The composition according to claim 76 for buccal use.

A3 dont

82. (New) The composition according to claim 76, wherein the composition is selected from the group consisting of tablets, pellets, powders, granules, and particulate material.

83. (New) The composition according to claim 76, in unit dosage form selected from the group consisting of a multiple unit dosage form and a single unit dosage form.

85. (New) The composition according to claim 83, wherein the unit dosage form comprises a daily dose.

86. (New) The composition according to claim 76, comprising an additional active drug substance.

87. (New) The composition according to claim 86, wherein the additional active drug substance is midodrine or a pharmaceutically acceptable salt thereof.

88. (New) The composition according to claim 87, wherein midodrine is selected from the group consisting of (±)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide, (+)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide, (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide and mixtures thereof.

89. (New) The composition according to claim 87, wherein midodrine is (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide.

90. (New) The composition according to claim 89, wherein at least 90% w/w of midodrine is

(-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide.

A3 cont

91. (New) The composition according to claim 82, wherein the composition is in the form of tablets having a disintegration time of at the most about 2.5 min.

92. (New) The composition according to claim 76, wherein the composition has a shelf life at room temperature of at least 6 months.

93. (New) The composition according to claim 76, wherein desglymidodrine is released from the composition with release kinetics corresponding to that of a plain release tablet.

94. (New) A composition according to claim 93, wherein the release kinetics of desglymidodrine from the composition is selected from the group consisting of a zero order, a first order release, a mixture of zero and first order release, a 1½ order, a second order, a third order and a fourth order release.

95. (New) A composition according to claim 93, wherein the composition is adapted to release desglymidodrine in such a manner that a relatively fast therapeutic effective concentration of desglymidodrine is obtained after administration of the composition.

96. (New) The composition according to claim 95, wherein the composition is adapted to release desglymidodrine to obtain an onset of action of at the most 15 minutes after administration.

97. (New) The composition according to claim 95, wherein the therapeutically effective concentration is obtained within 90 minutes from administration of the composition.

98. (New) The composition according to claim 95, wherein a peak plasma concentration of desglymidodrine is obtained about 1 min to 6 hours after administration.

A3 cont.

99. (New) The composition according to claim 76, wherein the composition is a controlled release composition.

100. (New) The composition according to claim 99, wherein the composition provides desglymidodrine in such a manner that a therapeutically effective plasma concentration of desglymidodrine is maintained for at least about 2 hours after administration after administration.

101. (New) The composition according to claim 99, wherein the composition is adapted to release desglymidodrine in such a manner that a therapeutically effective plasma concentration of desglymidodrine is maintained for about 4.5-14 hours.

102. (New) The composition according to claim 101, wherein the plasma concentration of desglymidodrine from the controlled release composition is maintained at a relatively constant level for about 4.5-14 hours.

103. (New) The composition according to claim 102, wherein the relatively constant level n is ± 60%, and wherein n is the plasma concentration in ng/ml and is monitored in healthy persons.

104. (New) The composition according to claim 99, wherein the release pattern of desglymidodrine from the controlled release composition when tested *in vitro* using a dissolution assay comprises:

release of 1-15% w/w from the composition within the first 30 minutes after the

start of the assay;

release of 10-35% (25%) w/w about 30 minutes after the start of the assay;
release of 15-40% (35%) w/w about 1 hour after the start of the assay;
release of 20-50% (39%) w/w about 2 hours after the start of the assay;
release of 20-55% (47%) w/w about 3 hours after the start of the assay;
release of 25-75% (53%) w/w about 4 hours after the start of the assay;
release of 30-74% (66%) w/w about 6 hours after the start of the assay;
release of 40-95% w/w (80%) about 8 hours after the start of the assay;
release of 65-100% (93%) w/w about 10 hours after the start of the assay; and
release of 75-110% (100%) w/w about 12 hours after the start of the assay.

A3 cont.

105. (New) The composition according to claim 104, wherein the composition contains midodrine or a pharmaceutically acceptable salt thereof and wherein the release rate of midodrine is substantially the same as the release rates of desglymidodrine.

106. (New) The composition according to claim 104, wherein the composition contains midodrine or a pharmaceutically acceptable salt thereof and wherein the release rate from the composition of the sum of midodrine and desglymidodrine calculated on a molar basis is substantially the same as the release rate for desglymidodrine.

107. (New) The composition according to claim 99, wherein the controlled release composition comprises at least two parts such as at least a first and a second part, each part contains desglymidodrine and the first part being adapted to release desglymidodrine in a controlled manner during the first 0-14 hours after oral intake and the second part being adapted to release desglymidodrine, starting at least 6 hours after oral intake.

108. (New) The composition according to claim 107, wherein at least one of the at least two

parts is present in the composition in the form of a multiplicity of individual units.

109. (New) The composition according to claim 107, wherein the two parts of the at least two parts are present in the composition in the form of a multiplicity of individual units and the two parts are in admixture.

A3 cont.

110. (New) The composition according to claim 108 or 109, wherein the individual units comprise pellets or minitablets.

111. (New) The composition according to claim 107, wherein at least one of the at least two parts comprises at least two different types of pellets, , the first type of pellets corresponding to the first part and the second type of pellets corresponding to the second part.

112. (New) The composition according to claim 107, wherein the composition is in the form of a multiple unit dosage form comprising at least two different types of minitablets, the first type of minitablets corresponding to the first part and the second type of minitablets corresponding to the second part.

113. (New) The composition according to claim 107, further comprising a third part adapted to release desglymidodrine relatively quickly from the composition.

114. (New) The composition according to claim 107, further comprising a fourth part adapted to release desglymidodrine from the composition 6-10 hours after administration.

115. (New) The composition according to claim 107, further comprising a fourth part adapted to release desglymidodrine from the composition in the colon after oral intake.

116. (New) A pharmaceutical kit comprising a composition comprising midodrine and a composition comprising a solid oral dosage form of desglymidodrine.

117. (New) The kit according to claim 116, wherein either or both compositions is a controlled release composition.

118. (New) A kit, comprising:

a fast onset solid oral dosage form of desglymidodrine formulated to provide a therapeutically effective concentration of desglymidodrine relatively quickly after administration, and

a controlled release pharmaceutical composition formulated to release desglymidodrine in a manner such that a therapeutically effective plasma concentration of desglymidodrine is maintained for at least about 2 hours.

119. (New) The kit according to claim 118, wherein the fast onset solid oral dosage form results in a peak or shoulder plasma concentration within 90 minutes upon administration.

120. (New) The kit according to claim 118, wherein the fast onset composition is in the form of a tablet which is a melt tablet or sublingual tablet.

121. (New) The kit according to claim 118, wherein the relatively fast onset composition is a buccal composition.

122. (New) The kit according to claim 118, wherein the fast onset solid oral dosage form comprises desglymidodrine in an amount of from 0.2 mg to 10 mg.

123. (New) A pharmaceutical kit comprising

a fast onset pharmaceutical composition comprising midodrine, formulated to provide a therapeutically effective concentration of midodrine relatively quickly after administration, and

a controlled release pharmaceutical composition formulated to release desglymidodrine in a manner such that a therapeutically effective plasma concentration of desglymidodrine is maintained for at least about 2 hours.

124. (New) A pharmaceutical kit comprising

a fast onset fast onset solid oral dosage form formulated to provide a therapeutically effective concentration of desglymidodrine relatively quickly after administration, and

a controlled release pharmaceutical composition formulated to release midodrine in a manner such that a therapeutically effective plasma concentration of midodrine is maintained for at least about 2 hours.

125. (New) A method for treating a patient suffering from conditions selected from the group consisting of orthostatic hypotension, syncope, urinary incontinence and urinary stress incontinence, the method comprising orally administering the composition according to claim 76 to a patient in need thereof.

126. (New) The method according to claim 125, wherein an administration of the composition takes place at wake-up time.

127. (New) The method according to claim 125, wherein an administration of the composition takes place in the morning.

128. (New) The method according to claim 125, wherein an administration of the composition takes place at in the middle of the day and is in the form of 1-2 tablets.

129. (New) The method according to claim 125, wherein the administration takes place 1-3 times daily.

130. (New) The method according to claim 125, wherein the administration takes place 1-2 times daily.

131. (New) The method according to claim 125, wherein the administration takes place once daily.

132. (New) A method according to claim 125, wherein a relatively fast onset composition comprising desglymidodrine is administered 1- 6 times daily.

133. (New) A method for treating a patient suffering from a condition selected from the group consisting of septic shock and other conditions responsive to α_1 receptor stimulation, the method comprising orally administering the composition of claim 76, to a patient in need thereof.

134. (New) The method according to claim 125 or 133, wherein desglymidodrine is selected from the group consisting of (±)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (± ST 1059), (+)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (+ ST 1059), (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059), and mixtures thereof.

135. (New) The method according to claim 134, wherein desglymidodrine comprises (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059).

136. (New) The method according to claim 135, wherein at least 90% w/w of

desglymidodrine is (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059).

137. (New) The method according to claim 125 or 133, wherein desglymidodrine is present in the form of a pharmaceutically acceptable salt selected from the group consisting of a salt formed between desglymidodrine and an inorganic acid and a salt formed between desglymidodrine and an organic acid.

138. (New) The method according to claim 125 or 133, wherein the composition is selected from the group consisting of tablets, pellets, powders, granules, and particulate material.

139. (New) The method according to claim 125 or 133, wherein the composition is in a unit dosage form selected from the group consisting of a multiple unit dosage form and a single unit dosage form.

140. (New) The method according to claim 139, wherein the unit dosage form comprises a daily dose.

141. (New) The method according to claim 125 or 133, wherein the composition comprises a additional active drug substance.

142. (New) The method according to claim 141, wherein the additional active drug substance is midodrine or a pharmaceutically acceptable salt thereof.

143. (New) The. method according to claim 142, wherein midodrine is selected from the group consisting of (±)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide, (+)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide, (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide and mixtures thereof.

144. (New) The method according to claim 143, wherein midodrine comprises (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide.

145. (New) The method according to claim 144, wherein at least 90% w/w of midodrine comprises (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide.

146. (New) The method according to claim 81, wherein the composition is in the form of tablets having a disintegration time of at the most about 2.5 min.

147. (New) The method according to claim 125 or 133, wherein the composition has a shelf-life at room temperature of at least 6 months.

148. (New) The method according to claim 125 or 133, wherein desglymidodrine is released from the composition with release kinetics corresponding to that of a plain release tablet.

149. (New) The method according to claim 148, wherein the release kinetics of desglymidodrine from the composition is selected from the group consisting of a zero order, a first order release, a mixture of zero and first order release, a 1½ order, a second order, a third order and a fourth order release.

150. (New) The method according to claim 149, wherein the composition is adapted to release desglymidodrine in such a manner that a relatively fast therapeutic effective concentration of desglymidodrine is obtained after administration of the composition.

151. (New) The method according to claim 150, wherein the composition is adapted to release desglymidodrine relatively fast in order to obtain an onset of action at the most 15

minutes after administration.

152. (New) The method according to claim 150, wherein the therapeutically effective concentration is obtained within 90 minutes from administration of the composition.

153. (New) The method according to claim 150, wherein a relatively fast peak plasma concentration of desglymidodrine is obtained within about 1 minute- 6 hours after administration.

154. (New) The method according to claim 125 or 133, wherein the composition is a controlled release composition.

155. (New) The method according to claim 125 or 133, wherein the composition is adapted to provide desglymidodrine in a manner such that a therapeutically effective concentration of desglymidodrine is maintained for at least about 2 hours after administration.

156. (New) The method according to claim 154, wherein the composition is adapted to release desglymidodrine in such a manner that a therapeutically effective plasma concentration of desglymidodrine is maintained for about 4.5-14 hours.

157. (New) The method according to claim 156, wherein the plasma concentration of desglymidodrine from the controlled release composition is maintained at a relatively constant level for about 4.5-14 hours.

158. (New) The method according to claim 157, wherein the relatively constant level n is ± 60%, and wherein n is the plasma concentration in ng/ml and is monitored in healthy persons.

159. (New) The method according to claim 154, wherein the release pattern of desglymidodrine in the controlled release composition when tested *in vitro* using a dissolution assay comprises:

release of 1-15% w/w from the composition within the first 30 minutes after the start of the assay;

release of 10-35% (25%) w/w about 30 minutes after the start of the assay;

release of 15-40% (35%) w/w about 1 hour after the start of the assay;

release of 20-50% (39%) w/w about 2 hours after the start of the assay;

release of 20-55% (47%) w/w about 3 hours after the start of the assay;

release of 25-75% (53%) w/w about 4 hours after the start of the assay;

release of 30-74% (66%) w/w about 6 hours after the start of the assay;

release of 40-95% w/w (80%) about 8 hours after the start of the assay;

release of 65-100% (93%) w/w about 10 hours after the start of the assay; and

release of 75-110% (100%) w/w about 12 hours after the start of the assay.

160. (New) The method according to claim 159, wherein the composition contains midodrine or a pharmaceutically acceptable salt thereof and wherein the release rate of midodrine from the controlled release composition is substantially the same as the release rate of desglymidodrine.

161. (New) The method according to claim 159, wherein the composition contains midodrine or a pharmaceutically acceptable salt thereof and wherein the release rate from the controlled release composition of the sum of midodrine and desglymidodrine calculated on a molar basis is substantially the same as the release rate for desglymidodrine.

162. (New) The method according to claim 154, wherein the controlled release composition

comprises at least a first and a second part, wherein each part contains desglymidodrine and wherein the first part releases desglymidodrine in a controlled manner during the first 0-14 hours after oral intake and the second part releases desglymidodrine, starting at least 6 hours after oral intake.

163. (New) The method according to claim 162, wherein at least one of the parts is present in the composition in the form of a multiplicity of individual units.

164. (New) The method according to claim 163, wherein the individual units comprise pellets or minitablets.

165. (New) The method according to claim 162, wherein the parts are in admixture.

166. (New) The method according to claim 162, wherein at least one of the parts comprises at least two different types of pellets.

167. (New) The method according to claim 162, wherein the first part comprises a first type of pellet and the second part comprises a second, different type of pellet.

168. (New) The method according to claim 162, wherein the first part comprises a first type of minitablet and the second part comprises a second, different type of minitablet.

169. (New) The method according to claim 162, wherein the composition further comprises a third part adapted to release desglymidodrine relatively quickly from the composition.

170. (New) The method according to claim 169, wherein the composition further comprises a fourth part adapted to release desglymidodrine from the composition 6-10 hours after

administration.

A3 cont.

171. (New) The method according to claim 169, wherein the composition further comprises a fourth part adapted to release desglymidodrine from the composition in the colon after oral intake.

Pending claims

Claims 1 to 75 are pending. Upon entry of this Amendment and Response, claims 1-75 are cancelled and claims 76- 171 are presented for examination. No new matter is added by this amendment. Support for the added claims is found throughout the specification and at least in the claims as originally filed.

Objection to Claims 6-69, 71 and 73

The Examiner has objected to claims 6-69, 71 and 73 for being improperly multiply dependent. Applicants submit the rejection is moot in view of the cancellation of the claims and respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claims 70, 72, 74, 75 Under 35 U.S.C. § 101

Claims 70, 72, 74, 75 are rejected under 35 U.S.C. § 101 for failing to state process steps. Applicant respectfully submits that the rejection is moot in view of the cancellation of the claims and respectfully requests that the rejection be reconsidered and withdrawn.

Rejection of Claims 4-5, 70, 72, 74, 75 Under 35 U.S.C. § 112 Second Paragraph

Claims 4-5, 70, 72, 74 and 75 are rejected under 35 U.S.C. § 112, second paragraph, for

failing to particularly point out and distinctly claim the invention. Applicants respectfully submit the rejection is moot in view of the cancellation of the claims and respectfully requests that the rejection be reconsidered and withdrawn.

The Invention

The invention relates to a solid oral dosage form of desglymidodrine. Although it was well known that desglymidodrine is an active metabolite of midodrine – no solid pharmaceutical composition for oral use has ever been suggested by a person skilled in art before the present invention. It was not believed that desglymidodrine could be used as an oral formulation because of stability problems, formulation problems, bioavailability problems, and fear of more pronounced adverse effects.

Surprisingly, the inventors discovered that, in fact, it was possible to provide a stable desglymidodrine-containing solid pharmaceutical composition for oral use. See, e.g., Example 28. The claimed compositions have the advantage of being immediately utilizable by the body, because an *in vivo* metabolic conversion of midodrine into desglymidodrine is avoided, Therefore, the possibility of variations in effect based on inter- or intra-individual variations in the metabolic conversion of desglymidodrine to midodrine is avoided when desglymidodrine is administered.

Rejection of Claims 1-5 Under 35 U.S.C. § 102(b) (Luzi)

Claims 1-5 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Luzi, et al. ("Luzi"). The Examiner states that Luzi discloses the hypertensive effects of desglymidodrine or ST-1059 in rats and racemic mixtures and enantiomeric forms of ST-1059. Applicants traverse

the rejection to the extent it would be applied to any of the newly added claims.

The newly added claims are drawn to orally administered solid forms of desglymidodrine. In contrast, Luzi describes the effect of enantiomers of midodrine and ST 1059 (desglymidodrine) in rats. The study is performed in anesthetized male rats, i.e. the doses of the test substance are given while the rats are asleep and therefore cannot be given orally in a solid form. Because the reference does not disclose each element of the claims, they are not properly rejected under section 102(b). Therefore, Applicants respectfully request that the rejections be reconsidered and withdrawn.

Rejection of Claims 1-5 Under 35 U.S.C. § 102(b) (JP 11139968)

Claims 1-5 are rejected under 35 U.S.C. § 102(b) as being anticipated by JP 11139968 ("JP '968"). Applicant respectfully traverses the rejection to the extent to which it would be applied to the newly added claims. JP '968 describes transdermal preparations. Such preparations are intended for application to the skin and are not suitable for use orally. Accordingly, Applicant submits that the disclosure of JP '968 does not anticipate the present invention as defined in the current set of claims, and respectfully requests that the rejection be reconsidered and withdrawn.

Rejection of Claims 1-5 Under 35 U.S.C. § 102(b) (Kontani)

Claims 1-5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kontani et al. (Kontani). Applicants traverse the rejection to the extent it would be applied to the added claims. Kontani describes intravenously injecting ST 1059 (desglymidodrine) in to develop a model for evaluating the effect of a drug on urethral leakage *in vivo*. No solid oral compositions are disclosed. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claims 70, 72, 74 and 75 Under 35 U.S.C. § 103(a)

Claims 70, 72, 74, and 75 are rejected under 35 U.S.C. § 103(a) as being obvious over Luzi, JP '968 or Kontani. The Examiner acknowledges that the references do not disclose methods of making the compositions but states that it would have been obvious to one of skill in the art to make the compositions disclosed by Luzi, JP '948, or Kontani using any method known in the art. Applicants traverse the rejection since none of the cited references disclose oral forms of desglymidodrine and therefore the references provide no teaching or motivation to manufacture such forms. However, solely to expedite prosecution in the instant application, Applicants have not included claims drawn to methods of making solid oral forms of desglymidorine in the newly added claims. Accordingly, Applicants submit that the rejection is improper and should be reconsidered and withdrawn.

Foreign Priority Claim

Applicants respectfully request that the Examiner acknowledge Applicants' foreign priority claim to PA 2000 00841, filed 26 May 2000 in Denmark. A certified copy of PA 2000 00841 was filed with the United States Patent and Trademark Office on August 23, 2001. Applicants additionally note their claim to priority to PCT/DK01/00214, filed March 29, 2001, and to U.S. Patent Application 09/823,093 also filed March 29, 2001, and respectfully request acknowledgement of the same.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with

Applicants' agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned agent of record.

Respectfully submitted,

Date: July 30, 2002

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